REMARKS

Claims 45-48 are pending in the application. Claim 45 has been amended to correct a typographical error in the claim. Claims 1-44 and 49-56 were previously canceled without prejudice. Applicants continue to reserve the right to pursue the subject matter of all canceled claims in one or more related applications.

No fees are believed to be due in connection with the filing of this Amendment after Final Rejection, however, should any fees be deemed necessary, the Commissioner is hereby authorized to deduct any necessary fees from Deposit Account No. 50-1050.

I. Preliminary Remarks

As a preliminary matter, a brief discussion of the procedural history in this case is necessary.

The Final Office Action being responded to in this submission was issued by the Office on January 23, 2006. The immediately preceding Office Action in this application was issued by the Office on November 10, 2005. Prior to receiving the Office Action dated November 10, 2005, Applicants filed a supplemental Response on November 14, 2005. As a result, Applicants have not had the opportunity to specifically address some of the issues raised by the Office in the Office Action dated November 10, 2005.

Consequently, although this submission is a response to the Final Office Action dated January 23, 2006, it will also address issues raised in the Office Action dated November 10, 2005.

II. Patentability Under 35 USC § 103

The Office continues to reject claims 45-48 under 35 USC § 103(a) as allegedly unpatentable over Beer et al., US 6,204,284 B1, for essentially the same reasons as set forth in the prior Office Actions issued by the Office in this case.

Applicants respectfully traverse the foregoing ground of rejection and submit that the subject matter of claims 45-48 is neither disclosed nor suggested by Beer et al., US 6,204,284 B1—based on the facts and reasoning set forth herein below, and as presented in the prior Amendments and Responses submitted by Applicants in this case, and in view of the entire record in this application.

A. The Applicable Case Law Supports the Patentability of Enantiomers of Known Compounds

It is well-established under the law that the disclosure of the racemate of a compound in the prior art does not negate the patentability of an optical isomer of the compound nor render the optical isomer of the compound obvious. For example, in the case of *In re May and Eddy*, 574 F.2d 1082, 197 USPQ 601, 607 (C.C.P.A. 1978), the court held that the nonaddictive properties of an optical isomer of an analgesic compound would have been unexpected to one skilled in the art and because of this, the optical isomer was nonobvious over its racemate and corresponding optical isomers.

More recently, in the case of *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 348 F. Supp. 2d 713 (N.D.W.V., 2004), the court held that claims directed to levofloxacin, the levorotatory [or (-)] optical isomer of the racemic compound ofloxacin, and methods of using levofloxacin to treat various diseases and conditions, were patentable over the racemic compound. In particular, the court held that the unexpected lower toxicity and higher activity of levofloxacin compared to the racemic compound rendered the levorotatory optical isomer and methods of using the levorotatory optical isomer patentable over the racemate.

In view of the foregoing, it is clear that the position taken by the Office that optical isomers of a compound are necessarily obvious over racemates of the compound is unsupportable.

B. The Case Law Cited by the Office does not Support the Obviousness of the Present Invention

The Office continues to cite the case of *In re Adamson*, 125 USPQ 233 (C.C.P.A., 1960) for the proposition that the motivation required by 35 USC § 103 is present in this case since "an isomer is often more reactive than the corresponding isomer or the racemate." (Office Action, p. 3) However, as previously and repeatedly noted by Applicants, the data set forth in the specification and in Attachment A of the Response filed by Applicants on November 14, 2005 indicates that the (-) isomer is not *more* reactive, but is in fact *less* reactive, than the racemic mixture. Therefore, *Adamson* is clearly inapplicable under the present circumstances.

Furthermore, the case of *In re Adamson* is readily distinguishable under the present circumstances. In *Adamson*, the isomer involved was about twice as active as the racemic

compound with respect to spasmolytic activity. In contrast, as discussed in detail below, the isolated (-) isomer has very different binding characteristics with respect to the dopamine reuptake site of the dopamine transporter, the norepinephrine uptake site of the norepinephrine transporter and the serotonin uptake site of the serotonin transporter when compared to the racemic mixture.

The case of *In re Lemin,* 141 USPQ 814 (C.C.P.A., 1964), previously cited by the Office, also does not support the position taken by the Office. In *Lemin,* the court found that a subgenus of compounds within a previously disclosed genus was in fact patentable, stating:

> Generally speaking, there is nothing unobvious in choosing "some" among "many" indiscriminately. (citation omitted) Here, however, the choice is based on a discovery by Lemin that some compounds, falling within a prior art genus, *have a special significance.* In short, Lemin has found that when the total number of carbon atoms is within the range of 5 to 12, the compounds will have *selective* and potent herbicidal action. (*Id.* at 815, *emphasis added*)

Similarly, as noted above and discussed in detail below, the isolated (-) isomer has a very different binding profile with respect to the dopamine reuptake site of the dopamine transporter, the norepinephrine uptake site of the norepinephrine transporter and the serotonin uptake site of the serotonin transporter when compared to the racemic mixture.

Clearly, the case law cited by the Office does not support the obviousness rejection issued by the Office in this case.

C. The Office Routinely Issues Patents Claiming Enantiomers of Compounds and their Use

The position taken by the Office is clearly inconsistent with its well-established practice of issuing patents claiming enantiomers of previously known compounds and their use.

For example, US Patent No. 6,864,257, issued March 8, 2005, contains claims to methods of using the dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, also known by the name of zopiclone, for inducing an effect selected from the group consisting of a hypnotic effect, a sedative effect and a tranquilizing effect.

U.S. Patent No. 6,844,355, issued January 18, 2005, contains claims to isomers of quinine and quinidine and their use in treating malaria.

U.S. Patent No. 6,534,508, issued March 18, 2003, contains claims to methods of treating microbial infections using the (S) optical isomer of lomefloxacin.

U.S. Patent No. 6,495,605, issued December 17, 2002, contains claims to pharmaceutical compositions containing and methods of treating pain using the (+) optical isomer of bupropion

U.S. Patent No. 6,147,077, issued November 14, 2000, contains claims directed to pharmaceutical compositions containing and methods of treating fungal diseases using optical isomers of hydroxyitraconazole.

In view of the foregoing, it is clear that the position of the Office in refusing to allow claims directed to methods of using (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane is unwarranted.

D. The Office has Properly Issued Patents in this Series of Cases

In the Final Office Action dated January 23, 2006, the Office makes the following statement:

> Applicant contends that since the instant compound was allowed in the parent case, methods of using it are allowable. This is generally true but not persuasive because the Office is not in the business of perpetuating its error. (Final Office Action, p. 3)

This disturbing comment is not only contrary to the facts in this case, it is also contrary to established law that the Office cannot continue to simply ignore.

The Office continues to disregard the fact that the (-) isomer of the present invention possesses substantially and unexpectedly different biological properties from the racemic mixture of Beer et al. In particular, as previously noted by Applicants, the data set forth in Tables 1, 2 and 3 on page 23 of the specification and the experiment set forth in Attachment A of the response filed by Applicants on November 14, 2005 clearly show that the racemic mixture and the isolated (-) isomer have very different binding profiles with respect to the dopamine reuptake site of the dopamine transporter, the norepinephrine uptake site of the norepinephrine transporter and the serotonin uptake site of the serotonin transporter. In this regard, the data in Table 1 on page 23 of the specification shows that while both the racemic mixture and (-) isomer have affinity for the dopamine reuptake site of the dopamine transporter, the racemic mixture actually has a *higher* binding affinity for this site than the (-) isomer, that is, the (-) isomer is not *more* reactive, but is in fact *less* reactive, than the racemic

mixture. Furthermore, the data in Tables 2 and 3 on page 23 of the specification indicates that the racemic mixture has affinity for the norepinephrine uptake site of the norepinephrine transporter and the serotonin uptake site of the serotonin transporter, while the (-) isomer had no measurable affinity for these sites. It must be emphasized that this is not simply a case "where an isomer is expected to be more active than the racemate or the other isomer." (Final Office Action, p. 3) Rather, in this instance, the (-) isomer has a completely different receptor binding profile when compared to the racemic mixture.

Additionally, experiments summarized in Attachment A of the Response filed by Applicants on November 14, 2005 and performed using more sensitive model systems further demonstrate the completely different receptor binding profile of the (-)-isomer of the present invention when compared with the racemic mixture of Beer et al. In these experiments, (-)-1-(3,4-dlchlorophenyl)-3-azabicyclo[3.1.0]hexane HCl, (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl were compared in dopamine, norepinephrine, and serotonin transporter binding and uptake assays using recombinant human receptors. In particular, the data in Table 1 of Attachment A referred to above indicate that the (-) isomer, the (+) isomer and the racemic mixture all have affinity for the dopamine uptake site as measured by binding and uptake. Conversely, the data in Table 1 show that the (+) isomer and the racemic mixture have substantially greater affinity for the serotonin and norepinephrine uptake sites than (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl as measured by both binding and reuptake. With respect to binding to the serotonin uptake site, there is a 3.93 fold difference between the (-) isomer and the racemic mixture and a 7.47 fold difference between the (-) isomer and the (+) isomer. With respect to binding to the norepinephrine uptake site, there is a 2.72 fold difference between the (-) isomer and the racemic mixture and a 3.93 fold difference between the (-) isomer and the (+) isomer. With respect to uptake at the serotonin uptake site, there is a 9.63 fold difference between the (-) isomer and the racemic mixture and a 10.8 fold difference between the (-) isomer and the (+) isomer. With respect to uptake at the norepinephrine uptake site, there is a 5.07 fold difference between the (-) isomer and the racemic mixture and a 4.52 fold difference between the (-) isomer and the (+) isomer.

Indeed, based in part on these differences, claims directed to (-)-1-(3,4-dlchlorophenyl)-3-azabicyclo[3.1.0]hexane (USPN 6,569,887) have been previously found to be patentable, as have claims directed to methods of treating or preventing disorders alleviated by inhibiting dopamine reuptake using (-)-1-(3, 4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane (USPN 6,716,868). These allowances were clearly proper and not in error, as implied by the

statement quoted above that "the Office is not in the business of perpetuating its error." (Final Office Action, p. 3)

Further, as previously noted, the position taken by the Office is inconsistent with established law. In particular, in the case of *In re Pleuddemann*, 15 USPQ2d 1738 (Fed. Cir. 1990), previously discussed in detail in the Response dated November 14, 2005 filed by Applicants, the Federal Circuit reversed a decision of the USPTO Board of Patent Appeals and Interferences, with the Federal Circuit holding that claims in a divisional case filed pursuant to a Restriction Requirement entered by the Office in the parent case and directed to methods of using compounds previously found patentable by the Office in the parent case were also patentable. This long-standing authority applies directly to the facts presented in the instant application. As a result of restriction requirements imposed by the Office, Applicants were compelled to prosecute compound claims directed to their novel (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexanes in separate applications from Applicants' novel methods of use employing these compounds. Applicants' compound claims, directed to (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexanes, have been previously examined and determined by the Office to be patentable (USPN 6,569,887). Additionally, the Office previously examined and allowed Applicants' distinct invention to generic methods of using (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane to treat disorders alleviated by inhibiting dopamine reuptake (USPN 6,716,868). Considering these antecedent dispositions by the PTO, in light of the authority presented above, Applicants are clearly entitled to additional claims employing their novel and unobvious (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexanes in the instantly recited methods.

E. Conclusion

In view of the foregoing, it is respectfully submitted that the rejection of claims 45-48 under 35 USC § 103(a) as allegedly unpatentable over Beer et al., US 6,204,284 B1 should be withdrawn.

III. Double Patenting

In the Office Action dated November 10, 2005, Claims 45-48 were rejected on the ground of nonstatutory obvious-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,716,868. However this rejection was not repeated in the Final Office Action dated January 23, 2006. As a result, it is appears that this rejection is not being maintained by the Office.

For the sake of completeness, however, Applicants hereby address this rejection and submit that it is improper since the claims of US Patent No. 6,716,868 directed to generic methods of treating disorders alleviated by inhibiting dopamine reuptake do not render obvious claims directed to treating or preventing particular diseases or conditions, in the present case addictive disorders. However, for the sole purpose of expediting prosecution of the present application, and without in any way admitting the propriety of the rejection, if required by the Office, Applicants would be willing to submit a Terminal Disclaimer that meets the requirements of 37 CFR 1.321.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at (206) 957-2489.

Dated this 20th day of March, 2006

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